Safety and efficacy of MPDL3280A (anti-PDL1) in combination with bevacizumab and/or chemotherapy in patients with locally advanced or metastatic solid tumors

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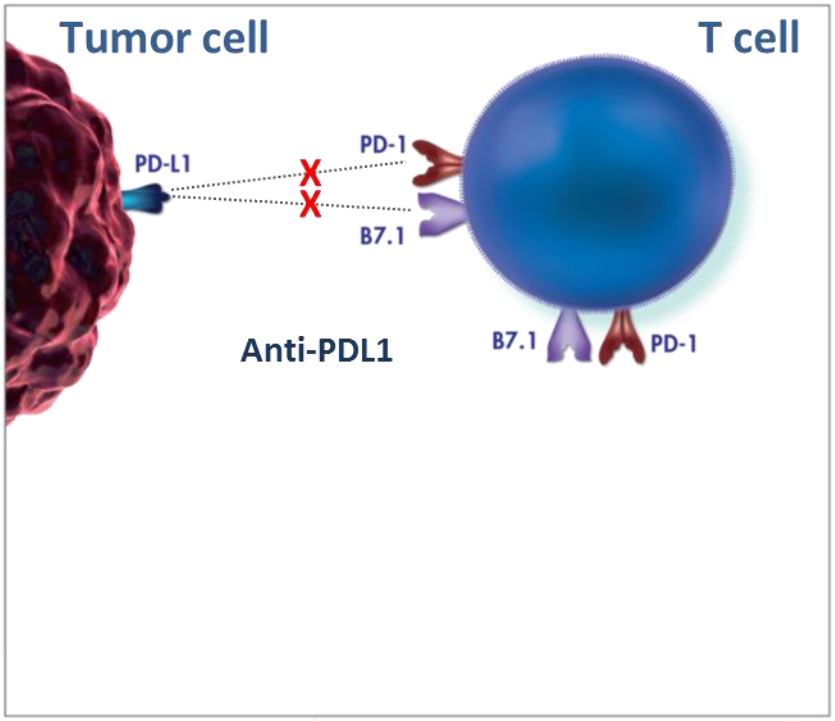
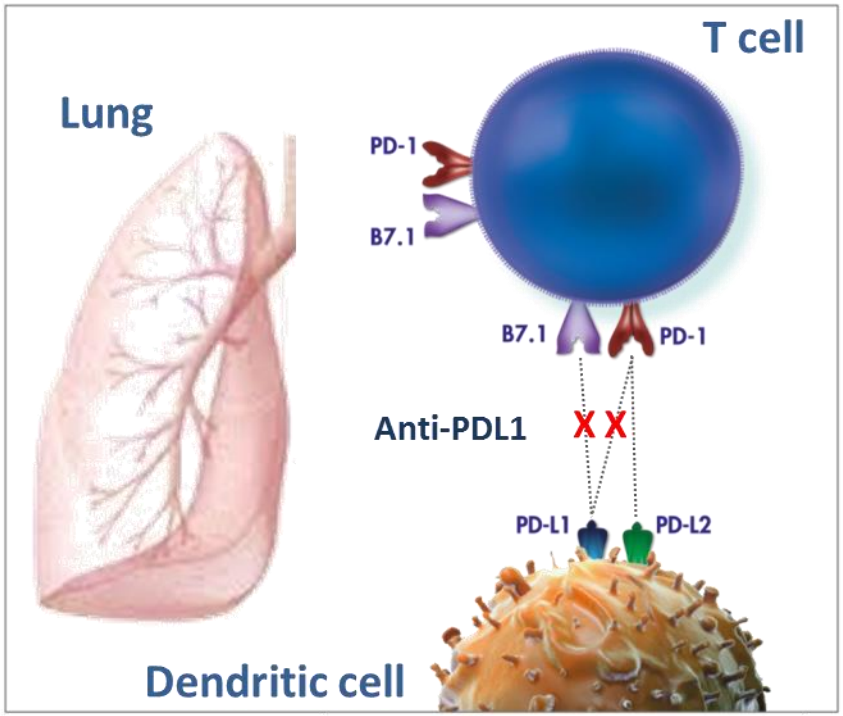
Disclosures

- Dr. Christopher Lieu
  - Consultant: Sanofi-Aventis

MPDL3280A is an Engineered Anti-PD-L1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1



- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming



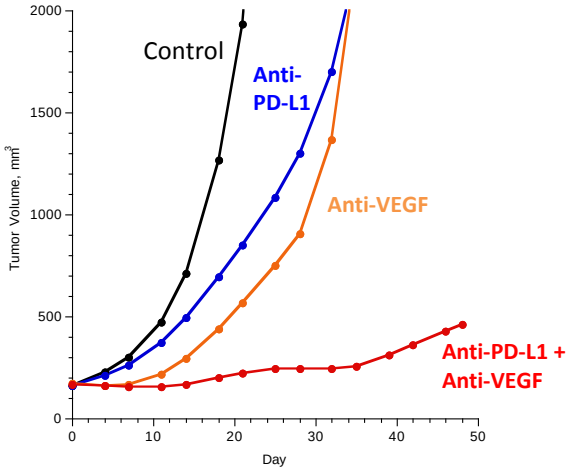
- MPDL3280A leaves the PD-L2/PD-1 interaction intact, maintaining immune homeostasis and potentially preventing autoimmunity

1. Akbari. *Mucosal Immunol.* 2010; 2. Matsumoto. *Biochem Biophys Res Commun.* 2008.

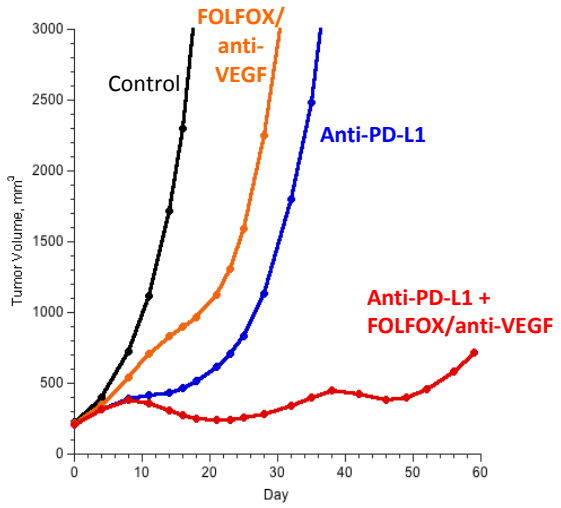
Rationale to Combine MPDL3280A With Bevacizumab and FOLFOX

- Anti-VEGF therapy has immunomodulatory properties
  - Increases trafficking of T cells into tumors[1,2]
  - Reduces suppressive cytokines and infiltrating Tregs and MDSCs[3,4]
- FOLFOX may have immunogenic effects
  - 5-FU reduces tumor-associated MDSCs and increases CD8 tumor-infiltrating lymphocytes[5]
  - Oxaliplatin induces immunogenic cell death (calreticulin exposure, release of ATP and HMGB1)[6,7]

Cloudman melanoma model[8]



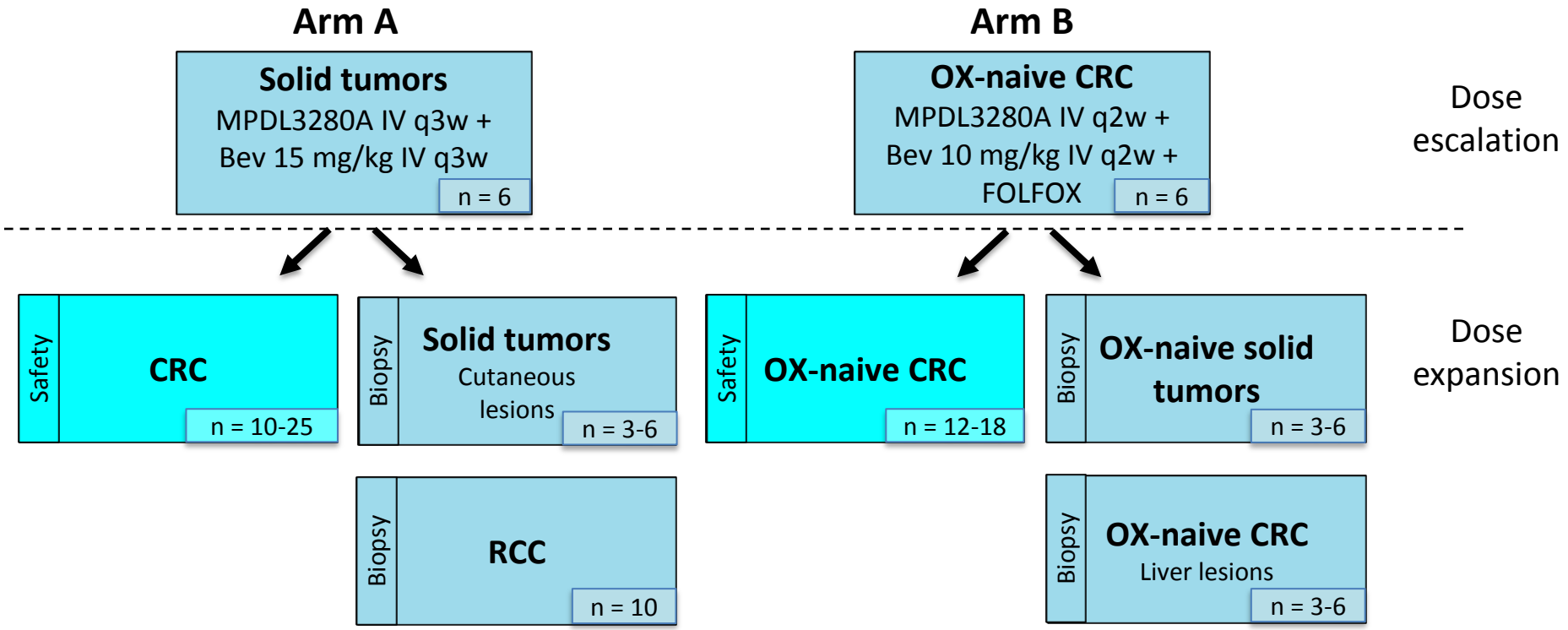
MC38 CRC model[8]



MDSC, myeloid-derived suppressor cell.

1. Manning. *Clin Cancer Res.* 2007. 2. Shrimali. *Cancer Res.* 2010. 3. Kutsmartsev. *J Immunol.* 2008. 4. Roland. *PLOS One.* 2009. 5. Vincent. *Cancer Res.* 2010. 6. Michaud. *Science*. 2011. 7. Tesniere. *Oncogene.* 2010. 8. Genentech, data on file.

Phase Ib Study Design



- Primary objectives: safety and tolerability, DLT and MTD
- Secondary objectives: preliminary anti-tumor activity and PK

n represent target enrollments.
Bev, bevacizumab; OX, oxaliplatin.

Baseline Characteristics

Arms A and B

Characteristics	Arm A n = 35	Arm B n = 36
Median age (range), y	56 (25-74)	57 (36-72)
Male	37%	47%
Tumor type		
CRC	40%	83%
RCC	34%	3%
Melanoma	11%	0
Breast	3%	6%
NSCLC	3%	0
Other	9%	8%
Prior systemic regimens		
0	29%	58%
1	9%	14%
2	3%	6%
≥ 3	60%	22%

RCC and CRC

Characteristics	Arm A RCC n = 12	Arm A CRC n = 14	Arm B CRC n = 30
Median age (range), y	64 (42-74)	56 (33-71)	57 (36-72)
Male	58%	29%	53%
Prior systemic regimens			
0	83%	0	70%
1-2	8%	0	17%
≥ 3	8%	100%	13%
Site of metastatic disease, n (%)			
Liver or lung	7 / 10 (70%)	14 (100%)	28 (93%)
Liver only	—	2 (14%)	8 (27%)
Other	8 / 10 (80%)	5 (36%)	6 (20%)

Safety evaluable population, data cutoff, July 7, 2014.

Adverse Events

- All Grade AEs attributed to MPDL3280A: Arm A 77%; Arm B 78%
- Grade 3 AEs attributed to MPDL3280A: Arm A 3%; Arm B 17%
- No Grade 4 AEs or deaths related to MPDL3280A

AEs Regardless of Attribution

AEs in ≥ 13 patients in at least 1 Arm, n (%)	Arm A, n = 35		Arm B, n = 36	
	All Grade	Grade 3-4	All Grade	Grade 3-4
All	35 (100%)	17 (49%)	36 (100%)	24 (67%)
Peripheral neuropathy	2 (6%)	0	25 (69%)	0
Fatigue	16 (46%)	0	24 (67%)	1 (3%)
Diarrhea	11 (31%)	0	21 (58%)	4 (11%)
Nausea	13 (37%)	0	18 (50%)	0
Temperature intolerance	1 (3%)	0	18 (50%)	0
Neutropenia	1 (3%)	1 (3%)	16 (44%)	14 (39%)
Decreased appetite	9 (26%)	0	15 (42%)	0
Pyrexia	13 (37%)	1 (3%)	9 (25%)	0
Vomiting	7 (20%)	0	13 (36%)	0

Grade 3-4 AEs Regardless of Attribution

AEs in ≥ 2 patients in at least 1 Arm, n (%)	Arm A, n = 35	Arm B, n = 36
	Grade 3-4	Grade 3-4
All	17 (49%)	24 (67%)
Neutropenia	1 (3%)	14 (39%)
Diarrhea	0	4 (11%)
Abdominal pain	3 (9%)	1 (3%)
Hypertension	3 (9%)	1 (3%)
Pneumonia	3 (9%)	0
AST increased	0	3 (8%)
ALT increased	0	3 (8%)
Hyperbilirubinemia	2 (6%)	0
Tumor pain	2 (6%)	0

Safety evaluable population, data cutoff, July 7, 2014.

Summary of Responses

MPDL3280A + Bevacizumab

Indication	n	ORR
1L RCC	10	40%
CRC	13	8%

Minimum follow-up in Arm A: 2.1 months for 1L RCC and 1.9 months for CRC

MPDL3280A + Bevacizumab + FOLFOX

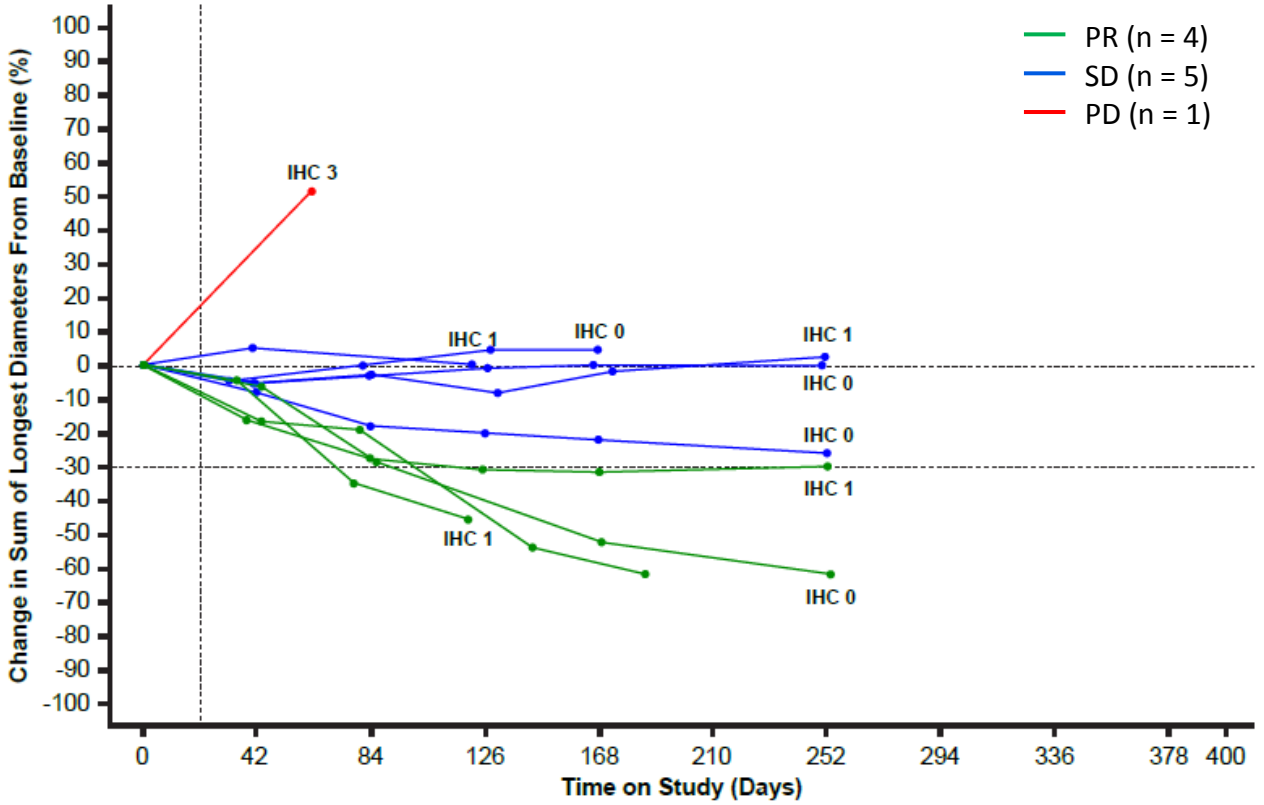
Indication	n	ORR
CRC	25	36%
1L CRC	18	44%

Minimum follow-up in Arm B: 2.2 months for CRC

- Responses in other cohorts
  - Arm A: melanoma (1/4 PR), breast cancer (1/1 PR)
  - Arm B: RCC (1/1 CR), breast cancer (1/2 PR)

Investigator-assessed unconfirmed response per RECIST v1.1.
Efficacy evaluable patients dosed by April 7, 2014, who had at least 1 scan; data cutoff, July 7, 2014.

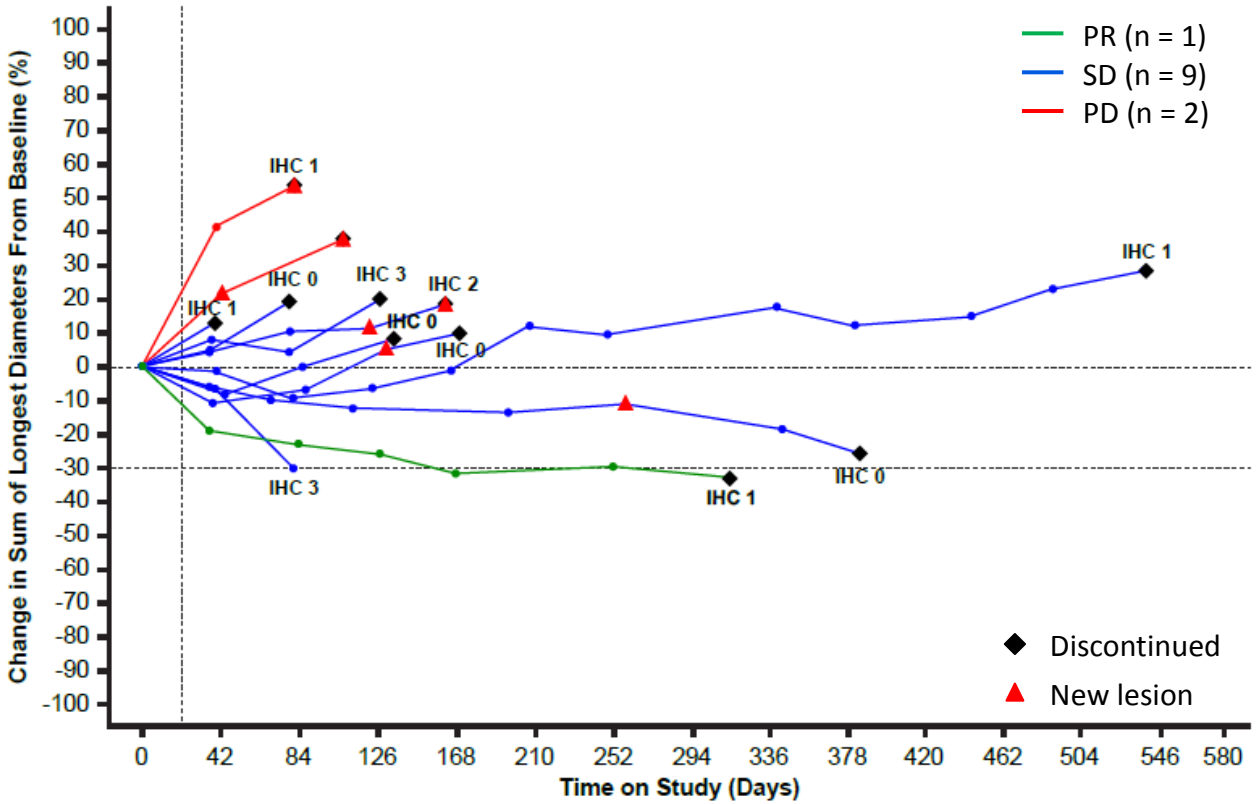
MPDL3280A + Bevacizumab: Tumor Burden Over Time in 1L RCC



- PR in 4 of 10 patients, additional 4 patients with SD ≥ 24 weeks
- 9 of 10 patients remain on study treatment
- Median duration of follow-up: 7.8 months

Investigator-assessed unconfirmed response per RECIST v1.1.
IHC 3, 2, 1, 0: ≥ 10%, ≥ 5% and < 10%, ≥ 1% and < 5%, < 1% tumor-infiltrating immune cells positive for PD-L1, respectively; IHC status not available for 1 patient.
Efficacy evaluable patients dosed by April 7, 2014, who had at least 1 scan; data cutoff, July 7, 2014.

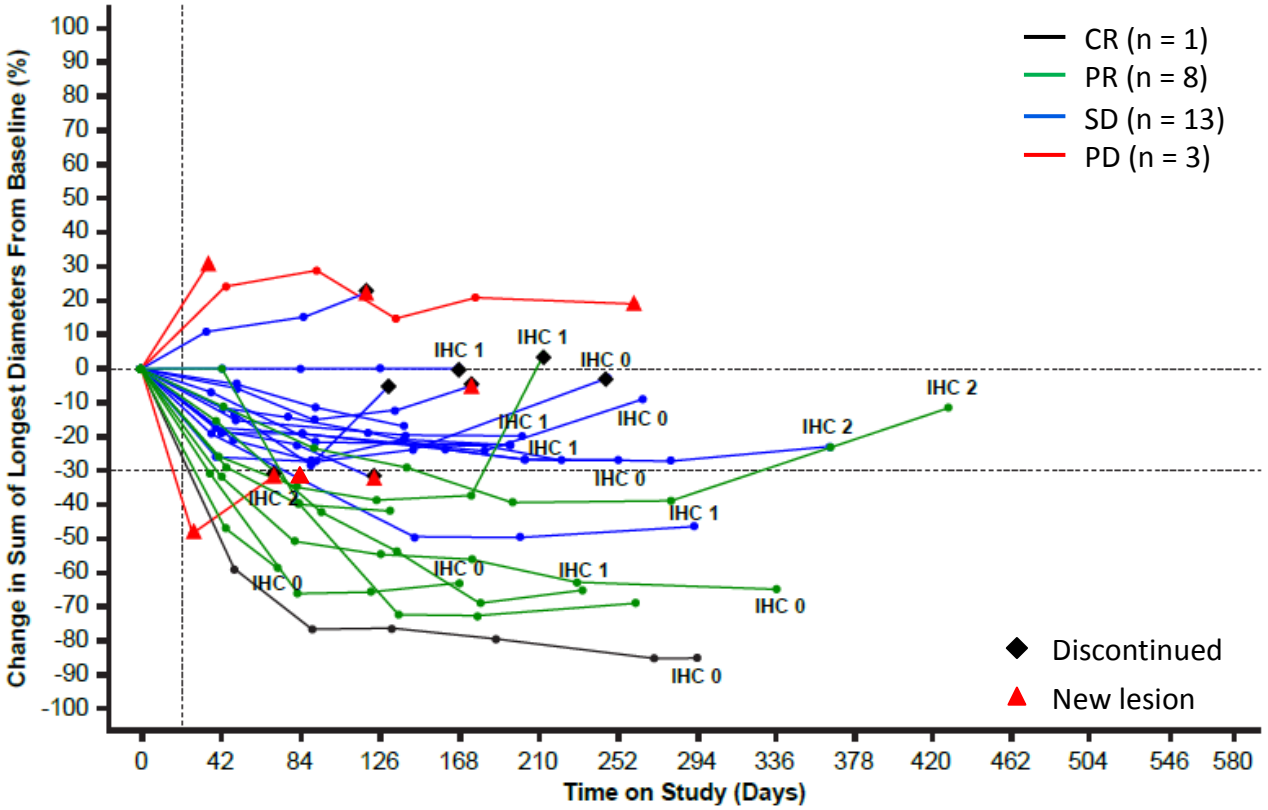
MPDL3280A + Bevacizumab: Tumor Burden Over Time in CRC



- SD ≥ 24 weeks in 2 patients
- Median duration of follow-up: 5.6 months

Investigator-assessed unconfirmed response per RECIST v1.1.
Does not include 2 patients: 1 patient did not have a scan post baseline and another patient had 1 target lesion that was not evaluable.
IHC 3, 2, 1, 0: ≥ 10%, ≥ 5% and < 10%, ≥ 1% and < 5%, < 1% tumor-infiltrating immune cells positive for PD-L1, respectively; IHC status not available for 1 patient.
Efficacy evaluable patients dosed by April 7, 2014, who had at least 1 scan; data cutoff, July 7, 2014.

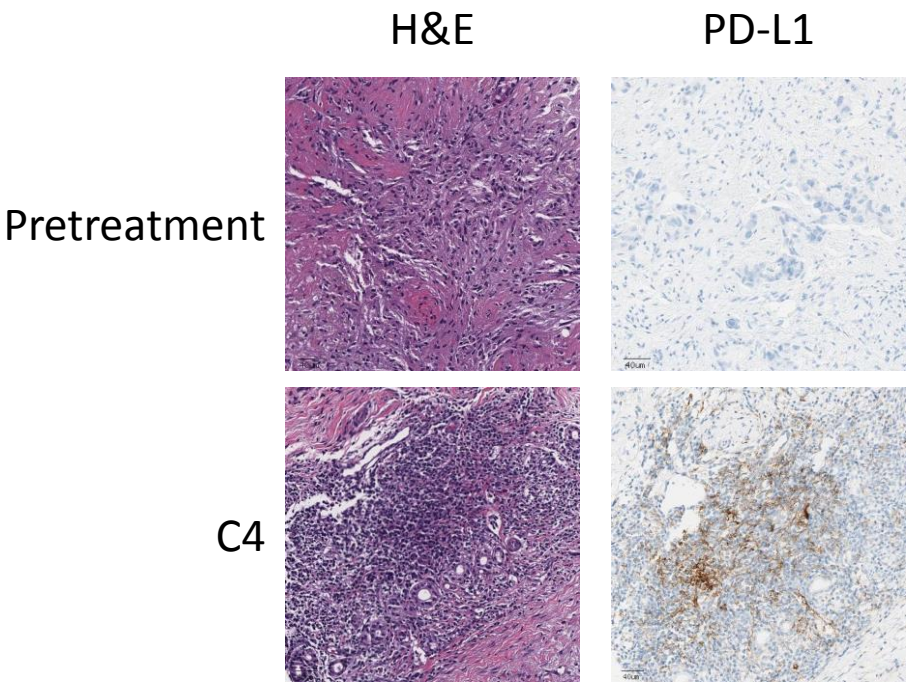
MPDL3280A + Bevacizumab + FOLFOX: Tumor Burden Over Time in CRC

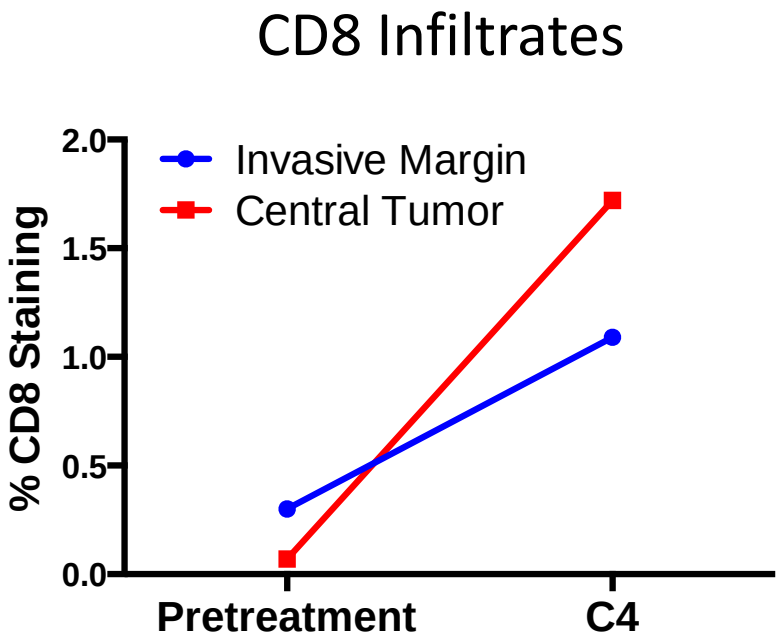


- SD ≥ 24 weeks in 8 patients
- Several patients had PRs as early as 6 weeks (first scan)
- Median duration of follow-up: 8.8 months

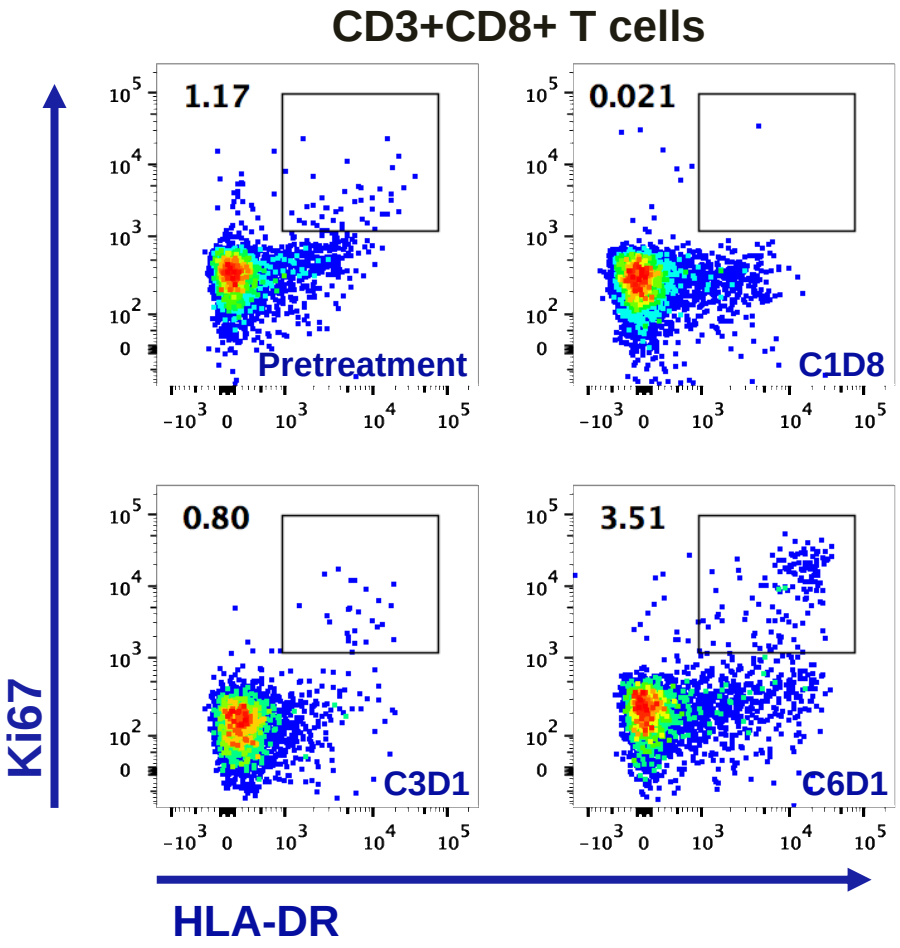
Investigator-assessed unconfirmed response per RECIST v1.1. For 1 patient, the sum of longest diameters could not be computed after RECIST overall assessment of SD because one of the target lesions was unevaluable at TA2. A new lesion was also identified at this visit.
IHC 3, 2, 1, 0: ≥ 10%, ≥ 5% and < 10%, ≥ 1% and < 5%, < 1% tumor-infiltrating immune cells positive for PD-L1, respectively; IHC status not available for 9 patients.
Efficacy evaluable patients dosed by April 7, 2014, who had at least 1 scan; data cutoff, July 7, 2014.

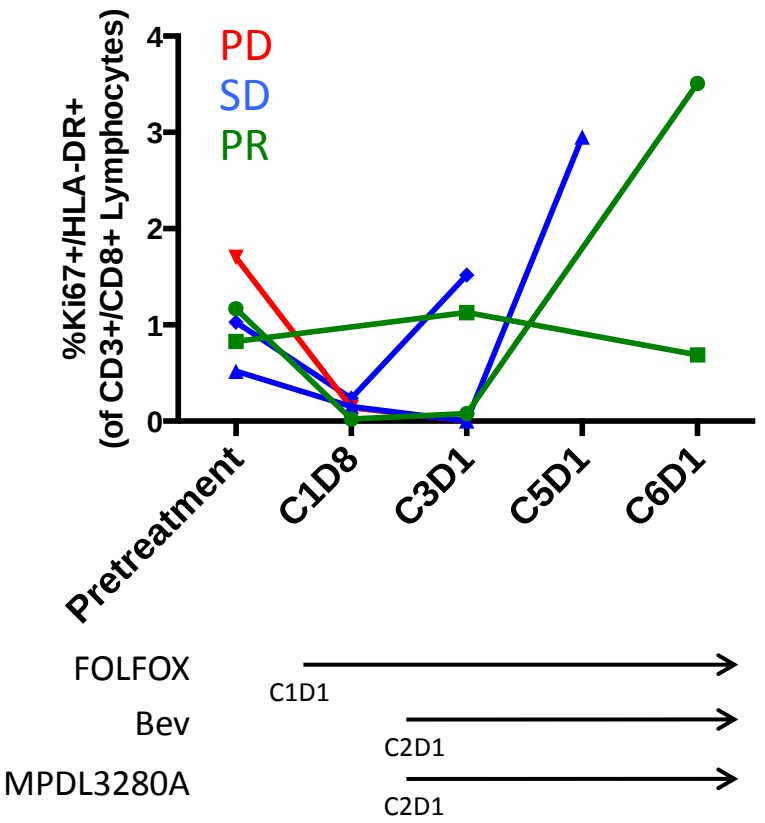
Increase in Tumor PD-L1 and CD8+ Infiltrates After MPDL3280A + Bevacizumab + FOLFOX in a CRC Patient





Decrease and Recovery of Activated T Cells in the Periphery After MPDL3280A + Bevacizumab + FOLFOX in a CRC Patient



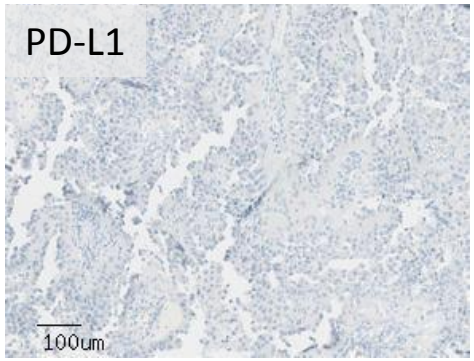


Dr. John Powderly, Carolina BioOncology.

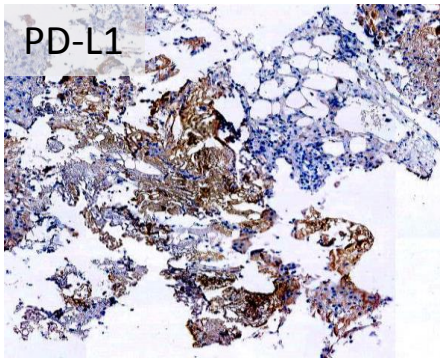
Increase in Tumor PD-L1 After MPDL3280A + Bevacizumab in a 1L RCC Patient and a Melanoma Patient

Arm A
1L RCC Patient[a]

Pretreatment



On Treatment



Arm A 1L RCC Patient[a]

Primary or Metastatic Tissue	Visit	IC %	IC Score	TC %
Metastatic	Pretreatment	<1	0	0
Metastatic	C3	10	3	40

Arm A Melanoma Patient[b]

Primary or Metastatic Tissue	Visit	IC %	IC Score	TC %
Metastatic	Pretreatment	<1	0	0
Metastatic	C3	8	2	50

[a] Dr. Johanna Bendell, Sarah Cannon Research Institute.
[b] Dr. John Powderly, Carolina BioOncology.

Conclusions

- MPDL3280A combination therapy with bevacizumab and bevacizumab + FOLFOX was well tolerated without exacerbation of bevacizumab or chemotherapy-associated adverse events
- Responses were observed in a variety of tumor types, including RCC and CRC
- Increased PD-L1 expression or activated peripheral T cells were observed with both treatment regimens
- Additional clinical trials of MPDL3280A combination therapies are planned/ongoing
  - A Phase II trial of MPDL3280A ± bevacizumab vs sunitinib in patients with previously untreated locally advanced or metastatic RCC is currently ongoing[1]
  - A randomized trial (MODUL) investigating MPDL3280A in the 1L mCRC maintenance setting is expected to start later this year[2]

1. www.clinicaltrials.gov. NCT01984242.
2. Schmoll, et al. ESMO 2014, abstract 612TiP.

Acknowledgments

The patients and their families

Participating Centers:

Johanna Bendell, Sarah Cannon Research Institute

Howard Hochster, Yale Cancer Center

Herbert Hurwitz, Duke University Medical Center

John Powderly, Carolina BioOncology

Gail Eckhardt, University of Colorado, Denver

Michael Pishvaian, Georgetown University

F. Stephen Hodi, Dana Farber Cancer Institute (also PI at additional sites: Beth Israel Deaconess Medical Center and Massachusetts General Hospital)